

General

Guideline Title

Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline.

Bibliographic Source(s)

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. [181 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); the difference between a "recommendation" and a "suggestion," and the definition of "best practice statements" are provided at the end of the "Major Recommendations" field.

Who Should Be Tested and How?

The Task Force recommends diagnostic testing to exclude primary adrenal insufficiency (PAI) in acutely ill patients with otherwise unexplained symptoms or signs suggestive of PAI (volume depletion, hypotension, hyponatremia, hyperkalemia, fever, abdominal pain, hyperpigmentation or, especially in children, hypoglycemia). (1|+++O)

The Task Force recommends confirmatory testing with the corticotropin stimulation test in patients with clinical symptoms or signs suggesting PAI when the patient's condition and circumstance allow. (1|++++)

In patients with severe adrenal insufficiency symptoms or adrenal crisis, the Task Force recommends immediate therapy with intravenous (iv) hydrocortisone at an appropriate stress dose prior to the availability of the results of diagnostic tests. (1|+++O)

Optimal Diagnostic Tests

The Task Force suggests the standard dose (250 µg for adults and children ≥2 y of age, 15 µg/kg for infants, and 125 µg for children <2 y of age) iv corticotropin stimulation (30 or 60 min) test over other existing diagnostics tests to establish the diagnosis of adrenal insufficiency. Peak cortisol levels below 500 nmol/L (18 µg/dL) (assay dependent) at 30 or 60 minutes indicate adrenal insufficiency. (2|++OO)

The Task Force suggests the low-dose (1 µg) corticotropin test for diagnosis of PAI only when the substance itself is in short supply. (2|++OO)

If a corticotropin stimulation test is not feasible, the Task Force suggests using a morning cortisol <140 nmol/L (5 µg/dL) in combination with adrenocorticotrophic hormone (ACTH) as a preliminary test suggestive of adrenal insufficiency (until confirmatory testing with corticotropin stimulation is available). (2|+OOO)

The Task Force recommends measurement of plasma ACTH to establish PAI. The sample can be obtained at the same time as the baseline sample in the corticotropin test or paired with the morning cortisol sample. In patients with confirmed cortisol deficiency, a plasma ACTH >2-fold the upper limit of the reference range is consistent with PAI. (1|+++O)

The Task Force recommends the simultaneous measurement of plasma renin and aldosterone in PAI to determine the presence of mineralocorticoid deficiency. (1|+++O)

The Task Force suggests that the etiology of PAI should be determined in all patients with confirmed disease. (For diagnostic workup, see Table 2 and Figure 1 in the original guideline document.) (Ungraded best practice recommendation)

Treatment of Primary Adrenal Insufficiency in Adults

Glucocorticoid Replacement Regimen

The Task Force recommends glucocorticoid therapy in all patients with confirmed PAI. (1|++++)

The Task Force suggests using hydrocortisone (15–25 mg) or cortisone acetate (20–35 mg) in two or three divided oral doses per day; the highest dose should be given in the morning at awakening, the next either in the early afternoon (2 h after lunch; two-dose regimen) or at lunch and afternoon (three-dose regimen). Higher frequency regimens and size-based dosing may be beneficial in individual cases. (2|++OO)

As an alternative to hydrocortisone, the Task Force suggests using prednisolone (3–5 mg/d), administered orally once or twice daily, especially in patients with reduced compliance. (2|+OOO)

The Task Force suggests against using dexamethasone for the treatment of PAI because of risk of Cushingoid side effects due to difficulties in dose titration. (2|++OO)

The Task Force suggests monitoring glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess. (2|+++O)

The Task Force suggests against hormonal monitoring of glucocorticoid replacement and to adjust treatment only based on clinical response. (2|+++O)

Mineralocorticoid Replacement in PAI

The Task Force recommends that all patients with confirmed aldosterone deficiency receive mineralocorticoid replacement with fludrocortisone (starting dose, 50–100 µg in adults) and not restrict their salt intake. (1|++++)

The Task Force recommends monitoring mineralocorticoid replacement primarily based on clinical assessment (salt craving, postural hypotension, or edema), and blood electrolyte measurements. (1|+++O)

In patients who develop hypertension while receiving fludrocortisone, the Task Force suggests reducing the dose of fludrocortisone. (2|+OOO)

If blood pressure remains uncontrolled, the Task Force suggests initiating antihypertensive treatment and continuing fludrocortisone. (2|+OOO)

Dehydroepiandrosterone Replacement

The Task Force suggests a trial of dehydroepiandrosterone (DHEA) replacement in women with PAI and low libido, depressive symptoms, and/or low energy levels despite otherwise optimized glucocorticoid and mineralocorticoid replacement. (2|++OO)

The Task Force suggests an initial period of 6 months of DHEA replacement. If the patient does not report a sustained, beneficial effect of replacement after 6 months, the DHEA should be discontinued. (2|++OO)

The Task Force suggests monitoring DHEA replacement by measuring morning serum DHEA sulfate (DHEAS) levels (aiming at the midnormal range) before the intake of the daily DHEA replacement dose. (2|++OO)

Treatment during Pregnancy

The Task Force suggests that pregnant patients with PAI be monitored for clinical symptoms and signs of glucocorticoid over- and under-replacement (e.g., normal weight gain, fatigue, postural hypotension or hypertension, hyperglycemia), with at least one review per trimester. (Ungraded best practice statement)

The Task Force suggests that, based on the individual clinical course, an increase in hydrocortisone dose should be implemented, in particular during the third trimester. (Ungraded best practice statement)

In pregnant women with PAI, The Task Force suggests using hydrocortisone over cortisone acetate, prednisolone, or prednisone (2|++OO) and recommend against using dexamethasone because it is not inactivated in the placenta. (1|++OO)

The Task Force recommends hydrocortisone stress dosing during the active phase of labor, similar to that used in major surgical stress. (1|++OO)

Treatment and Monitoring during Childhood

In children with PAI, the Task Force suggests treatment with hydrocortisone in three or four divided doses (total starting daily dose of 8 mg/m² body surface area) over other types of glucocorticoid replacement therapies, with doses adjusted according to individual need. (2|++OO)

In children with PAI, the Task Force suggests avoiding synthetic, long-acting glucocorticoids (e.g., prednisolone, dexamethasone). (2|++OO)

The Task Force suggests monitoring glucocorticoid replacement by clinical assessment, including growth velocity, body weight, blood pressure, and energy levels. (Ungraded best practice statement)

In children with PAI and confirmed aldosterone deficiency, the Task Force recommends treatment with fludrocortisone (starting dosage, 100 µg/d). For infants, the Task Force recommends sodium chloride supplements in the newborn period and up to the age of 12 months. (1|++OO)

Management and Prevention of Adrenal Crisis in Patients with PAI

The Task Force recommends that patients with suspected adrenal crisis should be treated with an immediate parenteral injection of 100 mg (50 mg/m² for children) hydrocortisone, followed by appropriate fluid resuscitation and 200 mg (50–100 mg/m² for children) of hydrocortisone/24 hours (via continuous iv therapy or 6 hourly injection); age- and body surface-appropriate dosing is required in children (see Table 3 in the original guideline document). (1|+++O)

If hydrocortisone is unavailable, the Task Force suggests prednisolone as an alternative. Dexamethasone is the least-preferred alternative and should only be given if no other glucocorticoid is available. (2|++OO)

For the prevention of adrenal crisis, the Task Force suggests adjusting glucocorticoid dose according to severity of illness or magnitude of the stressor. (2|++OO)

The Task Force suggests patient education concerning glucocorticoid adjustments in stressful events and adrenal crisis-prevention strategies including parenteral self- or lay-administration of emergency glucocorticoids. (Ungraded best practice statement)

The Task Force recommends that all patients should be equipped with a steroid emergency card and medical alert identification to inform health personnel of the need for increased glucocorticoid doses to avert or treat adrenal crisis and the need of immediate parenteral steroid treatment in the event of an emergency. (Ungraded best practice statement)

The Task Force recommends that every patient should be equipped with a glucocorticoid injection kit for emergency use and be educated on how to use it. (Ungraded best practice statement)

Additional Monitoring Requirement

The Task Force suggests that adults and children with PAI be seen by an endocrinologist or a healthcare provider with endocrine expertise at least annually. Infants should be seen at least every 3 to 4 months. (Ungraded best practice statement)

The Task Force suggests that PAI patients be evaluated annually for symptoms and signs of over- and under-replacement. (Ungraded best practice statement)

The Task Force suggests periodic screening for autoimmune diseases known to be more prevalent in PAI patients in whom autoimmune origin of PAI has not been excluded. The optimal frequency of screening is unknown but can be done annually. These conditions include thyroid disease, diabetes mellitus, premature ovarian failure, celiac disease, and autoimmune gastritis with vitamin B12 deficiency. (2|++OO)

The Task Force suggests patient education about increasing the dosage of glucocorticoids during intercurrent illness, fever, and stress. This

education includes identification of precipitating symptoms and signs and how to act in impending adrenal crisis. (Ungraded best practice statement)

The Task Force suggests genetic counseling for patients with PAI due to monogenic disorders. (Ungraded best practice statement)

Definitions

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Ungraded best practice statement: In this guideline, the Task Force made several statements to emphasize various monitoring and patient education actions needed to prevent the severe morbidity and mortality of adrenal crisis and reduce medication side effects. These were labeled as ungraded best practice statements. Direct evidence for these statements was either unavailable or not systematically appraised and was considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles, and these statements should not be considered as graded recommendations.

Clinical Algorithm(s)

An algorithm titled "Algorithm for the diagnostic approach to the patient with PAI" is provided in the original guideline document.

Scope

Disease/Condition(s)

Primary adrenal insufficiency (Addison's disease)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Pediatrics

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To addresses the diagnosis and treatment of primary adrenal insufficiency

Target Population

Children and adult patients (including pregnant women) with primary adrenal insufficiency

Interventions and Practices Considered

Diagnosis/Evaluation

1. Criteria for diagnostic testing for primary adrenal insufficiency (PAI)
2. Confirmatory testing with the corticotropin stimulation test
3. Immediate therapy with intravenous (iv) hydrocortisone at an appropriate stress dose prior to the availability of the results of diagnostic tests
4. Optimal diagnostic tests
 - Standard dose iv corticotropin stimulation test
 - Low-dose corticotropin test
 - Morning cortisol measurement in combination with adrenocorticotrophic hormone (ACTH) as a preliminary test
 - Measurement of plasma ACTH
 - Simultaneous measurement of plasma renin and aldosterone
 - Determination of etiology of PAI

Treatment/Management

1. Glucocorticoid replacement regimen
 - Hydrocortisone
 - Cortisone acetate
 - Prednisolone
 - Monitoring glucocorticoid replacement using clinical assessment (body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess)
2. Mineralocorticoid replacement
 - Fludrocortisone
 - Monitoring mineralocorticoid replacement through clinical assessment (salt craving, postural hypotension, or edema) and blood electrolyte measurements
 - Management of hypertension
3. Dehydroepiandrosterone (DHEA) replacement in women
4. Treatment and monitoring of glucocorticoid replacement during pregnancy
5. Treatment and monitoring of glucocorticoid replacement during childhood
6. Management and prevention of adrenal crisis
 - Parenteral injection of hydrocortisone
 - Fluid resuscitation
 - Prednisolone as an alternative
 - Dexamethasone as an alternative
 - Dosage adjustment

- Equipping patients with a steroid emergency card and medical alert identification
- Equipping patients with a glucocorticoid injection kit for emergency use

7. Additional monitoring requirements

- Frequency of visits
- Periodic screening for autoimmune diseases
- Patient education about increasing the dosage of glucocorticoids
- Genetic counseling

Note: The following were considered but not recommended: dexamethasone and hormonal monitoring of glucocorticoid replacement.

Major Outcomes Considered

- Diagnostic accuracy of high-dose adrenocorticotrophic hormone (ACTH) versus low-dose ACTH stimulation tests for the initial diagnosis
- Severe adrenal insufficiency symptoms or adrenal crisis
- Quality of life
- Bone mineral density
- Number of adrenal crises
- Final adult height
- Morbidity and mortality
- Medication side effects

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Task Force commissioned two systematic reviews (see the "Availability of Companion Documents" field) and developed an a priori protocol that included a specific search strategy, inclusion and exclusion criteria, and methods of evidence synthesis. The two reviews summarized data on patients with both primary and secondary adrenal insufficiency; however, the Task Force used data derived from patients with primary adrenal insufficiency (PAI) because this was the target population of this guideline.

Diagnostic Performance of Adrenocorticotrophic Hormone (ACTH) Stimulation Tests for the Diagnosis of Adrenal Insufficiency. Systematic Review and Meta-analysis

Search Strategy

A comprehensive search of several databases from each database's earliest inception to 2014 Week 08, any language was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for adrenal insufficiency. The actual strategy is detailed as Appendix 1 in the systematic review document.

The Effect of Different Glucocorticoid Replacement Regimens on Patient-Important Outcomes in Patients with Adrenal Insufficiency

The reviewers included original prospective and retrospective comparative and noncomparative studies that enrolled patients with adrenal insufficiency and reported the outcomes of interest.

The search included a comprehensive search of several databases, no language restriction was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced Mayo clinic librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for the studies

(see Appendix 1 in the systematic review document for detailed search strategy).

Abstracts and titles that resulted from executing the search strategy were independently evaluated by two reviewers for potential eligibility and the full text versions of all potentially eligible studies were obtained. Two reviewers working independently considered the full text reports for eligibility. Disagreements were resolved by the study primary investigator.

Number of Source Documents

Diagnostic Performance of Adrenocorticotrophic Hormone (ACTH) Stimulation Tests for the Diagnosis of Adrenal Insufficiency. Systematic Review and Meta-analysis

Secondary Adrenal Insufficiency

The reviewers identified 30 studies assessing the diagnostic performance of either the high or low dose ACTH stimulation test for the diagnosis of secondary adrenal insufficiency. A figure showing a summary of the selection process is provided in the systematic review (see the "Availability of Companion Documents" field).

Primary Adrenal Insufficiency

Five studies looking at the diagnostic performance of the high-dose ACTH stimulation test for the diagnosis of primary adrenal insufficiency were found. Eight studies that evaluated the high-dose ACTH were excluded due to lack of a predefined gold standard, report of equivocal results for the gold standard or the use of a gold standard not compatible with the inclusion criteria.

The Effect of Different Glucocorticoid Replacement Regimens on Patient-Important Outcomes in Patients with Adrenal Insufficiency

The extensive search yielded 2726 references for abstract screening. 24 studies were included in this systematic review (see Figure 1 in the systematic review document).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of the Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Task Force commissioned two systematic reviews (see the "Availability of Companion Documents" field) and developed an a priori protocol that included a specific search strategy, inclusion and exclusion criteria, and methods of evidence synthesis. The two reviews summarized data on patients with both primary and secondary adrenal insufficiency; however, the Task Force used data derived from patients with primary adrenal insufficiency (PAI) because this was the target population of this guideline.

Diagnostic Performance of Adrenocorticotrophic Hormone (ACTH) Stimulation Tests for the Diagnosis of Adrenal Insufficiency. Systematic Review and Meta-analysis

Study selection and data extraction were done in duplicate. Diagnostic estimates from included studies were pooled using the random effects model as implemented in Meta disc software package. See the full systematic review for details of the analysis.

Risk of Bias

Using the Quality Assessment of Diagnostic Studies (QUADAS)-2 instrument, studies overall had moderate risk of bias. This conclusion is mainly driven by unclear or inappropriate patient selection and referral bias leading to high prevalence. Otherwise, the studies had low risk of bias in the domains of index test, reference standard, and flow and timing.

The Effect of Different Glucocorticoid Replacement Regimens on Patient-Important Outcomes in Patients with Adrenal Insufficiency

Using a standardized form two reviewers independently extracted data from each study and later reconciled differences, if present. Reviewers determined the methodological quality of studies and collected descriptive, methodological and outcome data.

Risk of Bias

Risk of bias was assessed using the Cochrane tool for randomized control trials and the Newcastle Ottawa scale for observational studies. In summary, there was a moderate risk of bias in the included randomized controlled trials. There was incomplete data analysis in 3 studies and allocation was not concealed or unclear in all of the studies. The observational studies were generally of good quality and the authors tried to minimize the risk of bias. Samples were representative in most studies with no baseline imbalance; nearly all the studies adjusted for at least one important confounder and most of the studies had adequate follow up period.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Participants

The Task Force included a chair, selected by The Clinical Guidelines Subcommittee of the Endocrine Society, eight additional clinicians experienced with the disease, a methodologist, and a medical writer. The co-sponsoring associations (European Society of Endocrinology and the American Association for Clinical Chemistry) had participating members.

Evidence

This evidence-based guideline was developed using the Grading of Recommendations, Assessment Development and Evaluation (GRADE) system to determine the strength of recommendations and the quality of evidence.

Consensus Process

The evidence used to formulate recommendations was derived from two commissioned systematic reviews as well as other published systematic reviews and studies identified by the Task Force.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Ungraded best practice statement: In this guideline, the Task Force made several statements to emphasize various monitoring and patient education actions needed to prevent the severe morbidity and mortality of adrenal crisis and reduce medication side effects. These were labeled as ungraded best practice statements. Direct evidence for these statements was either unavailable or not systematically appraised and was considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles, and these statements should

not be considered as graded recommendations.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed and approved sequentially by the Endocrine Society's Clinical Guidelines Subcommittee and Clinical Affairs Core Committee, members responding to a web posting, and the Endocrine Society Council. At each stage, the Task Force incorporated changes in response to written comments.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Even with treatment, the health-related quality of life (HRQoL) in patients with Addison's disease receiving standard replacement therapy is often reduced. Moreover, long-term HRQoL in these patients appears to be inversely related to the delay in establishing the diagnosis after disease onset, emphasizing the importance of recognizing the disease early.
- Prevention of the severe morbidity and mortality of adrenal crisis and reduction of medication side effects
- Dehydroepiandrosterone (DHEA) replacement in primary adrenal insufficiency (PAI) with a single oral dose has been shown to restore circulating levels of androgen precursors and androgens back to the normal range. In addition, some (but not all) studies have shown that DHEA replacement in adrenal insufficiency may improve HRQoL and mood, with reduced depression and anxiety scores.

Potential Harms

- Caution is required because adrenocortical function test results may be severely affected by rare conditions such as cortisol-binding globulin (CBG) deficiency, glucocorticoid resistance, and hypersensitivity.
- Retrospective studies of patients taking higher doses of glucocorticoids in some cases, including prednisolone or dexamethasone, appear to show a tendency to adverse metabolic consequences including weight gain, dyslipidemia, and diabetes mellitus.
- Symptoms and signs of glucocorticoid over-replacement are weight gain, insomnia, and peripheral edema. Insufficient dosing is characterized by nausea, poor appetite, weight loss, lethargy, and hyperpigmentation.
- Signs and symptoms of inadequate mineralocorticoid replacement include poor weight gain, salt craving, dehydration, hyponatremia with hyperkalemia, and elevated plasma renin activity or concentration. Excessive mineralocorticoid replacement results in hypertension and suppressed plasma renin.
- Primary hypertension may also be present in primary adrenal insufficiency (PAI). Assessment of the hypertensive PAI patient should involve an evaluation of not only the fludrocortisone dose but also the glucocorticoid dose because overtreatment with either preparation can lead to hypertension.

- Cortisone acetate may be used instead of hydrocortisone; however, caution should be used because 11 β -hydroxysteroid dehydrogenase type 1 activity is variable in childhood, and it is uncertain whether the hydrocortisone dose equivalency used in adults applies in children.

Contraindications

Contraindications

- Primary hypertension may also be present in primary adrenal insufficiency (PAI). Diuretics should be avoided. Aldosterone receptor blockers such as spironolactone and eplerenone are contraindicated.
- Glucocorticoid preparations that can be used in pregnancy are hydrocortisone, cortisone acetate, prednisolone, and prednisone; dexamethasone is usually contraindicated because it is not inactivated by placental 11 β -hydroxysteroid dehydrogenase type 2 and thus crosses the placenta to the fetus.
- Licorice and grapefruit juice potentiate the mineralocorticoid effect of hydrocortisone and should be avoided.
- Rectal suppositories (prednisolone 100 mg suppository) or enemas (prednisolone 20 mg/100 mL or hydrocortisone acetate enema 10%) have been successfully used but should not be used with diarrhea.

Qualifying Statements

Qualifying Statements

- Clinical Practice Guidelines are developed to be of assistance to endocrinologists and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016 Feb;101(2):364-89. [181 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Feb

Guideline Developer(s)

The Endocrine Society - Professional Association

Source(s) of Funding

Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Guideline Committee

Diagnosis and Treatment of Primary Adrenal Insufficiency Task Force

Composition of Group That Authored the Guideline

Task Force Members: Stefan R. Bornstein (*Chair*), Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, David J. Torpy

Financial Disclosures/Conflicts of Interest

The Endocrine Society maintains a rigorous conflict of interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the Clinical Guidelines Subcommittee (CGS) before the

members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (e.g., stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Financial Disclosures of the Task Force*

Stefan R. Bornstein, MD, PhD (Chair)—Financial or Business/Organizational Interests: Novo Nordisk, Boehringer Ingelheim; Significant Financial Interest or Leadership Position: none declared.

Bruno Allolio, MD—Financial or Business/Organizational Interests: European Society of Endocrinology; Significant Financial Interest or Leadership Position: Boehringer Ingelheim (Consultant).

Wiebke Arlt, MD, DSc, FRCP, FMedSci—Financial or Business/Organizational Interests: European Society of Endocrinology, Society for Endocrinology, Diurnal Limited, Janssen Pharmaceutical, Atterocor; Significant Financial Interest or Leadership Position: none declared.

Andreas Barthel, MD, MSc—Financial or Business/Organizational Interests: DGE (German Endocrine Society); Significant Financial Interest or Leadership Position: none declared.

Andrew Don-Wauchope, MB, BCh, MD, FRCP Edin, FCPATH, FRCPath, FRCPC—Financial or Business/Organizational Interests: Institute for Quality Management in Healthcare, Canadian Society for Clinical Chemistry, American Association of Clinical Chemistry; Significant Financial Interest or Leadership Position: Canadian Association of Medical Biochemists (Past President).

Gary D. Hammer, MD, PhD—Financial or Business/Organizational Interests: ISIS Pharmaceutical, Orphagen, HRA Pharma, Embara; Significant Financial Interest or Leadership Position: Atterocor (Founder, Owner, Consultant).

Eystein Husebye, MD, PhD—Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: ViroPharma/Shire (Lecturer).

Deborah P. Merke, MS, MD—Financial or Business/Organizational Interests: Diurnal Limited; Significant Financial Interest or Leadership Position: none declared.

M. Hassan Murad, MD, MPH—Financial or Business/Organizational Interests: Mayo Clinic, Division of Preventive Medicine; Significant Financial Interest or Leadership Position: none declared.

Constantine A. Stratakis, MD, DSc—Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: none declared.

David J. Torpy, MBBS, PhD, FRACP—Financial or Business/Organizational Interests: Novartis; Significant Financial Interest or Leadership Position: None declared.

*Financial, business, and organizational disclosures of the Task Force cover the year prior to publication.

Disclosures prior to this time period are archived.

Guideline Endorser(s)

American Association of Clinical Chemistry, Inc. - Professional Association

European Society of Endocrinology - Medical Specialty Society

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from [The Endocrine Society Web site](#) .

Availability of Companion Documents

The following are available:

- Ospina NS, Al Nofal A, Bancos I, Javed A, Benkhadra K, Kapoor E, Lteif AN, Natt N, Murad HM. ACTH stimulation tests for the diagnosis of adrenal insufficiency: systematic review and meta-analysis. J Clin Endocrinol Metab. 2016 Feb;101(2):427-34. Available to subscribers from the [Journal of Clinical Endocrinology & Metabolism Web site](#) .
- Al Nofal A, Bancos I, Khalid B, Javed A, Ospina NS, Kapoor E, Muthusamy K, Lteif A, Natt N, Murad MH. The effect of different glucocorticoid replacement regimens on patient-important outcomes in patients with adrenal insufficiency. Research methodology summary report. Knowledge and Evaluation Research Unit, Mayo Clinic-Preliminary report.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 15, 2016. The information was not verified by the guideline developer.

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